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Supersized kidneys: Lessons from the preclinical obese kidney

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The worldwide prevalence of obesity continues to rise. Obesity has been shown to increase the risk of both the development and the progression of renal failure, even after correction for other comorbid conditions. The ability of nephrologists to intervene will require greater understanding of obesity's renal physiologic effects. Kidney biopsies and functional studies performed on morbidly obese patients without overt renal disease who presented for bariatric surgery have helped to elucidate the earliest obesity-related structural and functional responses.

Kidney International (2008) **73**, 909–910. doi:10.1038/ki.2008.42

It's a fat world after all. According to the most recent statistics (2003–2004) from the National Center for Health Statistics of the Centers for Disease Control and Prevention, two-thirds (66.3%) of American adults are overweight or obese.[1] For adults age 20–39 the prevalence of overweight or obesity is 57.1%, increasing to a startling 73.1% for those in the 40-to-59-year age group and 71.0% for those over age 60.[1] The epidemic is not limited to the United States. According to the World Health Organization, the prevalence of obesity worldwide has increased from approximately 200 million adults in 1995 to over 300 million adults in 2000.[2] Recent estimates indicate that over one billion adults, roughly one-fifth of the world population, are overweight or obese.[2]

From those statistics has followed a dramatic increase in the prevalence of metabolic syndrome, including hypertension, dyslipidemia, and insulin resistance. What is more, obesity has been found to compound the risk for chronic kidney disease in diverse renal settings. Hsu *et al.* have demonstrated that with each gradient increase in body mass index (BMI), there is a greater relative risk of end-stage renal disease: 1.87 for overweight individuals, 3.57 for those with class 1 obesity, 6.12 for those with class 2, and 7.07 for those with class 3 (morbid) obesity.[3] These associations remain strong even after adjustment for obesity-related comorbid conditions such as diabetes and hypertension. Similarly, Fox *et al.* have reported a 23% increase in the odds of development of chronic kidney disease for each standard deviation increase in BMI, even after adjustment for age, sex, baseline glomerular filtration rate, smoking, and diabetes.[4] A recent metaanalysis has concluded that obesity is a strong risk factor for the development and progression of chronic kidney disease.[5] Obesity has well-recognized effects on renal hemodynamics that promote progressive renal disease. Nephrologists' ability to intervene will depend on a better understanding of the physiologic basis for this increased risk.

Serra *et al.*[6] (this issue) provide insight into the early obesity-induced renal physiologic and pathologic responses. Historically, the first studies on obesity-related renal disease were case reports at autopsy in morbidly obese patients.[7] Later, biopsy-based studies of obesity-related focal sclerosis helped to define the clinical-pathologic features of this entity.[8] All these studies focused on patients with clinically overt renal disease. The study by Serra *et al.*[6] has the advantage of performing systematic renal biopsies on all morbidly obese patients without overt renal manifestations who presented for bariatric surgery to a center in Barcelona, Spain. Thus, it offers a rare, if not unique, window on the preclinical obese kidney in patients who would otherwise not have reached a threshold for renal biopsy.

Not surprisingly, the investigators found a variety of renal structural abnormalities in patients with morbid obesity and no overt clinical renal disease. Glomerular hypertrophy (glomerulomegaly) was present in 38% of morbidly obese patients, compared with only 2.5% of normal-BMI controls. There was also an increased prevalence of focal segmental glomerulosclerosis, global glomerulosclerosis, mesangial sclerosis, mesangial hypercellularity, and podocyte hypertrophy. By multivariate analysis, only BMI was associated with development of glomerular lesions, independently of hypertension and hyperglycemia, which were present in 46% and 14% of patients, respectively. Thus, among patients with morbid obesity (BMI >40 kg/m^2), the degree of elevation of BMI per se confers increased risk of developing glomerular lesions. These findings are consistent with recent evidence that the quantity of excess adipose tissue itself may exert systemic effects through the secretion of a variety of hormones and cytokines, including leptin, adiponectin, tumor necrosis factor-α, angiotensinogen, interleukin-6, and C-reactive protein.[9]

One of the most interesting findings to emerge from this study is that glomerulomegaly was more prevalent in extremely obese patients with sleep apnea (51%) than without sleep apnea (28%). This difference was statistically significant, suggesting a potential pathogenetic link between sleep apnea and the development of glomerular hypertrophy. Sleep apnea activates the sympathetic nervous system, promoting systemic hypertension and activation of the renin–angiotensin axis, in turn leading to glomerular capillary hypertension.[10,11] In fact, patients with

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obesity-related glomerulopathy have been noted to have hyperplasia of the juxtaglomerular apparatus on renal biopsy.[8] Obese patients have elevations of both renal plasma flow and glomerular filtration rate that exceed those of controls by 31% and 51%, respectively,[12] thereby promoting glomerular capillary hypertension. Taken together, these studies suggest that weight loss could have a beneficial effect on preservation of renal function, independent of other interventions such as pharmacologic blockade of the renin–angiotensin system or control of systemic hypertension. Drastic weight loss after bariatric surgery has led to reductions in glomerular filtration rate and albuminuria within 12 months of surgery in most morbidly obese patients, supporting the potential reversibility of these functional alterations.[13] The results of the study by Serra *et al.*[6] also suggest that aggressive treatment of sleep apnea syndrome, particularly in obese patients in whom weight loss is unattainable, is likely to have a beneficial effect on proteinuria and renal function.

The authors also found that 41% of extremely obese patients had microalbuminuria and 4% had albuminuria (defined as albuminuria >300 and <500 mg per 24 hours). Thus, nearly half had early functional markers of glomerular disease. Longer prospective follow-up of such patients is needed to determine whether the subset with microalbuminuria is more at risk for development of obesity-related focal segmental glomerulosclerosis, analogous to the role of microalbuminuria in detection of diabetic patients at risk for development of overt diabetic nephropathy.

Some additional comments regarding the study by Serra *et al.*[6] are worth considering. First, because no patients with class 1 (BMI 30–34.9) or class 2 (BMI 35–39.9) obesity were included, the study cannot address the effects of these lower grades of obesity on the development of glomerular disease. Second, the definition of 'glomerular lesions' (that is, mesangial sclerosis, mesangial proliferation, or podocyte hypertrophy) is nonspecific and difficult to quantify, making it unlikely to achieve high interobserver agreement. Third, the finding of mesangial sclerosis is also common in smokers,[14] who constituted half of the extremely obese patients in this study. Finally, a very interesting but underemphasized statistic is that 9 of the 139 morbidly obese patients screened for bariatric surgery were excluded from the study because they had renal insufficiency or proteinuria (>500 mg per day). Although the sample size is small, these data suggest a 6.5% prevalence of overt renal disease among patients with morbid obesity.

In summary, the kidneys of morbidly obese patients without overt clinical renal disease harbor a variety of predominantly glomerular lesions. Even when clinically silent, the physiologic effects of obesity can produce structural renal changes. We must conclude that those patients who develop overt proteinuria and renal insufficiency are just the tip of the iceberg in a disease of epidemic proportions.

REFERENCES

1. Ogden CL, Carroll MD, Curtin LR *et al.* Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA* 2006; **295**: 1549–1555.
2. The world health report 2002: reducing risks, promoting healthy life. World Health Organization, Geneva, Switzerland, 2002.
3. Hsu CY, McCulloch CE, Iribarren C *et al.* Body mass index and risk for end-stage renal disease. *Ann Intern Med* 2006; **144**: 21–28.
4. Fox CS, Larson MG, Leip EP *et al.* Predictors of new-onset kidney disease in a community-based population. *JAMA* 2004; **291**: 844–850.
5. Wang Y, Chen X, Song Y *et al.* Association between obesity and kidney disease: a systematic review and meta-analysis. *Kidney Int* 2008; **73**: 19–33.
6. Serra A, Romero R, Lopez D *et al.* Renal injury in the extremely obese patients with normal renal function. *Kidney Int* 2008; **73**: 947–955.
7. Cohen AH. Massive obesity and the kidney. *Am J Pathol* 1975; **81**: 117–130.
8. Kambham N, Markowitz GS, Valeri AM *et al.* Obesity-related glomerulopathy: an emerging epidemic. *Kidney Int* 2001; **59**: 1498–1509.
9. Hutley L, Prins J. Fat as an endocrine organ: relationship to the metabolic syndrome. *Am J Med Sci* 2005; **330**: 280–290.
10. Peppard PE, Young T, Palta M *et al.* Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000; **342**: 1378–1384.
11. Nieto FJ, Young TB, Lind BK *et al.* Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA* 2000; **283**: 1829–1836.
12. Chagnac A, Weinstein T, Korzets A *et al.* Glomerular hemodynamics in severe obesity. *Am J Physiol Renal Physiol* 2000; **278**: F817–F822.
13. Navarro-Diaz M, Serra A, Romero R *et al.* Effects of drastic weight loss after bariatric surgery on renal parameters in extremely obese patients: long-term follow-up. *J Am Soc Nephrol* 2006; **17**: S213–S217.
14. Nasr SH, D'Agati VD. Nodular glomerulosclerosis in the non-diabetic smoker. *J Am Soc Nephrol* 2007; **18**: 2032–2036.